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UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE INCORPORATED,

Plaintiff,

v.

VYSIS, INC.,

Defendant.

No. 99-CV-2668H AJB

REPLY DECLARATION OF DR. KARY B. MULLIS IN SUPPORT OF GEN-PROBE'S MOTION FOR PARTIAL SUMMARY JUDGMENT OF NON-INFRINGEMENT UNDER THE DOCTRINE OF EQUIVALENTS

Date: November 19, 2001
Time: 10:30 a.m.
Place: Court Room 1

THE HONORABLE MARILYN L. HUFF

I, Kary B. Mullis, residing at Newport Beach, California, do hereby declare as follows:

1. I make this declaration in response to the Supplemental Opposition filed by defendant Vysis.

DOCTRINE OF EQUIVALENTS

2. Gen-Probe's "Transcription Mediated Amplification" (TMA) is a method of sequence-specific nucleic acid amplification. It is not a method of non-specific amplification and it does not use techniques of non-specific amplification.

3. There are very major and substantial differences between methods of specific amplification, such as TMA, and methods of non-specific amplification. This fact is well known to those of ordinary skill in the art. These two distinct methods of amplification do not perform substantially the same function in substantially the same way to achieve substantially the same result, and this fact is well known to those of ordinary skill in the art. That is why one method is called "specific amplification" and the other method is called "non-specific amplification."

4. I have read the declaration of David Persing in opposition to Gen-Probe's motion for summary judgment.

5. Dr. Persing's declaration does not state that there are only insubstantial differences between methods of specific amplification, such as TMA, and methods of non-specific amplification. Nothing in Dr. Persing's declaration would lead one skilled in the art to reach such a conclusion.

6. Dr. Persing's declaration does not meaningfully address the "triple identity" test of whether TMA and non-specific amplification "perform substantially the same function in substantially the same way to achieve substantially the same result."

7. Persons of ordinary skill in the art know and understand that even specific nucleic acid amplification techniques have some degree of non-specificity. They also know that this ancillary and limited degree of non-specificity is immaterial to determining whether specific amplification techniques are equivalent to non-specific amplification. When persons of ordinary skill in the art employ methods of sequence-specific amplification, such as TMA and PCR, those methods are extremely specific as compared with amplification using random hexamer primers and

non-specific enzymes. As I stated repeatedly in my deposition, the difference in specificity is like the difference between night and day. PCR and TMA are both 1,000,000 times more specific than any non-specific amplification system, and the consequences of this difference are both substantial and absolute.

8. The fact that TMA and PCR may result in some very limited amount of amplification of non-target sequences does not render those sequence-specific methods the equivalent of non-specific amplification methods with random hexamer primers and non-specific enzymes, which are deliberately designed to be *totally* non-specific.

9. The non-specific products of PCR and TMA do not affect the overall specificity of the processes. The primary product of specific amplification is identified by its precisely defined length and the presence of amplified internal target sequences. Spuriously amplified sequences, when they occur, are only rarely the same size as the target-specific product. Furthermore, spuriously amplified sequences, when they occur, do not contain internal sequences that are homologous to target-specific hybridization probes. Therefore, it is easy to distinguish the spuriously-amplified products.

10. Although TMA and PCR may generate limited amounts of non-target sequences, these specific amplification methods function to increase exponentially both the ***absolute*** and ***relative*** amount of the sequence of interest, as intended. PCR, without a target capture step, is useful for detecting biologically significant sequences in clinical laboratories. TMA, without a target capture step, is useful for detecting biologically significant sequences in clinical laboratories. Non-specific amplification methods, such as those suggested in the '338 patent, are not useful diagnostic methods, with or without a target capture step.

11. Dr. Persing's declaration suggests that TMA and the non-specific amplification method of Example 5 of the '338 patent are equivalent because each results in the creation of a double-stranded DNA, and this double-stranded DNA constitutes "the same result" from each process. This statement is not true. The mere fact that both products are double-stranded DNA is immaterial to one skilled in the art. What is important is the content of the double-stranded DNA. The double-stranded product of the amplification method of Example 5 would be a heterogeneous

collection of fragments containing a mixture of sequences present in the original sample. Each of these fragments would have at its 5' end a random hexamer primer of unknown sequence. Whether or not the collection of fragments contains any sequences of a specific target, such as a pathogen that might be present in a clinical sample, is unknown. I am not aware of any reports in the literature showing that the method of example 5 has ever been actually carried out successfully. In contrast, PCR and TMA produce discrete products of known size and composition. Both the absolute and relative amounts of the specific target sequence are increased millions-fold, allowing the detection of even a single molecule of target within millions of molecules of non-target sequence. The success of diagnostic tests using specific amplification methods such as PCR and TMA is well documented in the literature

12. Dr. Persing suggests that the random primers used in the non-specific amplification method of Example 5 will bind only to target-specific sequences if the target capture step of the '338 patent is first used to eliminate polynucleotides other than the target. I understand that in determining whether two methods constitute "equivalents," one must consider the methods by themselves, and may not consider "the invention as a whole," e.g., other steps that are involved in the claimed invention. Furthermore, there is likewise no evidence I am aware of in the literature that the combination of the target capture procedure set forth in example 5 with the non-specific amplification methods of that example can be used to detect small amounts of target within a clinical sample. Again, Dr. Persing fails to cite a single scientific paper in which the target capture method set forth in example 5 has been shown to purify a target sequence present in small amounts in clinical samples. Nor does he cite a single scientific paper in which the combination of the target capture procedure of example 5 and the non-specific amplification methods of example 5 have been used successfully in a clinical diagnostic assay (or in any other way). In contrast, Gen-Probe, Roche, and Organon Teknika, among others, have developed and marketed successful clinical assays using specific amplification methods, both in combination with target capture and without target capture. There is simply no evidence that the same results have ever been achieved, period.

13. Vysis' supplemental opposition presents only a portion of my testimony on the issue of Example 5 of the '338 patent. In the rest of my testimony, when asked about the "alternative" use of a capture probe as a specific primer in Example 5, I pointed out that such use would not result in specific amplification:

> Q. But in fact, you could do it [the method of Example 5] repeatedly with that single capture probe and get specific linear amplification, right?
>
> A. Specific, in the sense of more specific than doing it with hexamers, but certainly not specific in regard to doing it with respect to doing it with two different oligos [primers] that both had to be involved [as in PCR or TMA]. That's a very big difference. It's a difference like 10 to the 7th and 10 to the 14th, which is a big difference. It's a lot of zero's...

(Mullis Deposition at 96.) The amount of specificity added by using a capture probe as a primer under the conditions of Example 5 is minor. The product of such a method is unlikely to result in significant sequence products for the following reasons: (1) the capture probe will bind non-specifically to DNA in the sample (i.e., the "capture" step is not 100% specific); (2) the enzymatic synthesis suggested in Example 5 to replicate the captured DNA may terminate at a variety of positions, resulting in non-uniform products; and (3) the RNA transcription step of the method is non-specific.

14. Let me be clear: one skilled in the art would conclude that Example 5 does not result in specific amplification. Adding some slight specificity to a non-specific method does not change the method into a "specific" amplification method. That is undoubtedly why the introduction to Example 5 states: "In this example, both non-specific replication of target DNA and transcription of that DNA are used to amplify capture target DNA." In contrast, a specific amplification method such as PCR, uses specific primers and biochemical steps to specifically amplify defined portions of target nucleic acids.

15. Vysis also suggests that my note attached as Exhibit "F" by Vysis to its supplemental opposition demonstrates that I believe TMA is equivalent to non-specific amplification techniques. That statement is false and the inferences Vysis attempts to draw from that note are inaccurate. As I repeatedly stated during my deposition, and as reaffirmed herein, I

unequivocally reject any view that one of ordinary skill in the art would consider TMA to be equivalent to non-specific amplification. The fact that I believe TMA may be less specific than PCR does not change that view. TMA is a method of sequence-specific amplification. Furthermore, as I testified in my deposition, I have no information about why Gen-Probe includes a target capture step in its blood testing products. Finally, I understand that Gen-Probe offers for sale several FDA-approved diagnostic products that use TMA to specifically amplify nucleic acids, but do not use a target capture step.

16. None of the statements in Dr. Persing's declaration is material to considering whether there are substantial differences between TMA and non-specific methods of amplification. I reaffirm the statements made in my declaration in support of Gen-Probe's motion. One of ordinary skill in the art would conclude that there are substantial differences between Gen-Probe's TMA method and the non-specific amplification methods described and claimed in the '338 patent. Sequence-specific amplification methods such as TMA do not perform substantially the same function in substantially the same way to achieve substantially the same result as non-specific methods of amplification.

LITERAL INFRINGEMENT

17. I have read the order of this Court dated June 20, 2001 granting partial summary judgment on the issue of literal infringement following the Court's construction of the claims of the '338 patent. From a scientific perspective, the reasoning of the Court in that order is absolutely correct. I entirely agree with and support the Court's reasoning.

18. I have read Vysis' November 8, 2001 Supplemental Opposition. I have noted that Vysis states: "Dr. Mullis ... views the claims of the '338 patent as encompassing specific in vitro amplification techniques." Let the record be crystal clear, despite the efforts of Vysis' counsel to confuse things. It is my opinion that as of December 21, 1987 a person of ordinary skill in the art would have understood the term "amplifying" as used in the claims of the '338 patent to mean amplifying by use of the non-specific amplification methods described in the '338 specification. Reading the specification, a person of ordinary skill in the art would not have understood the term "amplifying" as used in the claims of the '338 patent to mean amplifying by use of sequence-

specific amplification methods incorporating specific primers, specific promoters, and/or specific enzymes.

19. I have read the declaration of Joseph O. Falkinham III dated April 30, 2001 submitted by Gen-Probe in support of its prior motion for summary judgment on the issue of literal infringement. I entirely agree with the statements set forth in Dr. Falkinham's declaration.

20. Vysis suggests that my January 23, 2001 notes attached as Exhibit "A" by Vysis to its supplemental opposition demonstrate that I believe the claims of the '338 patent literally include specific amplification. This statement is false. The January 23, 2001 notes were not written on the subject of claim interpretation. As I stated in my deposition, I wrote those comments in my very early reading of the '338 patent to demonstrate that the claims of the '338 patent were obvious and not novel. I wrote those comments before I considered the issue of claim interpretation, and on an entirely different subject. Vysis has simply taken a single document, written on the separate subject of patent invalidity, out of context. Vysis' position that the claims literally include specific amplification is, as I said at my deposition, "an incredibly horrible thing to have to defend." (Mullis Deposition at 116.)

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct and that this declaration is executed at Newport Beach, California on November __, 2001.

Kary B. Mullis